International Journal of Obesity (1997) 21, 935–940
 0307–0565/97 $12.00

Familial risk ratios for extreme obesity: implications for mapping human obesity genes

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OBJECTIVE: To determine familial risk ratios for extreme obesity to aid in the design of obesity linkage studies.
DESIGN: Family study of obesity
SUBJECTS: 2349 first-degree relatives (parents and siblings) of 840 probands who are members of the National Association to Advance Fat Acceptance (NAAFA) and 5851 participants of the first phase of the National Health and Nutrition Examination Survey III.
METHODS: Computed age–gender standardized risk ratios (SRRs) for obesity in relatives categorized by the level of obesity in the index case (proband).
MEASUREMENT: Body mass index (BMI) (kg/m^2)
RESULTS: The risk of extreme obesity (BMI $\geq$ 40) in relatives of extremely obese women (BMI $\geq$ 40) was more than five times greater than in the population; furthermore, the risk of obesity in relatives was approximately linearly associated with the degree of obesity in the proband. The risk of thinness in relatives of obese individuals was substantially lower than in the general population.
CONCLUSION: Because the familial risk ratio for extreme obesity is higher than for moderate levels of obesity, the number of families required to achieve adequate statistical power in gene mapping studies of obesity can be reduced substantially by focusing on family members of extremely obese individuals (BMI $\geq$ 40).

Keywords: familial risk ratio; lambda; body mass index; obesity; linkage; family study

Introduction

Traditional methods in genetic epidemiology, such as family, twin and adoption studies have identified genetic susceptibility as a major contributing factor to the familial aggregation of obesity;[1] these studies have provided the impetus for a new area of investigation designed to map and characterize genes which predispose humans to be obese. The identification of such genes will be challenging, in large part because the expression of obesity may depend on numerous factors: multiple obesity-susceptibility loci (and their potential interactions), reduced penetrance and environmental variables such as availability of a calorically dense diet. Several segregation studies report results that are consistent with major gene influence on obesity.[1,2,3] Although some genes eventually may be found to have large effects on some obesity phenotypes in humans, already more than 70 genes or chromosome regions have been implicated as having some role in obesity in humans or animal models.[4]

The difficulties facing studies designed to identify obesity-susceptibility genes in humans are evident from the inconsistencies in results across studies. Differences may be due to:

(1) actual locus heterogeneity (for example, different genes or combinations of genes leading to obesity in different populations);
(2) inadequate statistical power to detect polygenic loci with small effects (high rates of false negatives);
(3) low prior probability that any particular gene will have a measurable effect in a particular sample (high rates of false positives) or
(4) environmental heterogeneity (for example, differences in exposure to risk and protective factors).

Furthermore, it has been shown that replication of susceptibility loci for a complex trait requires a longer period of time (for example, a larger sample size) than the initial detection of linkage.[5]

Given these challenges facing linkage studies of obesity, it is necessary to employ a study design that maximizes the feasibility of localizing obesity-susceptibility loci and that allows for replication of those findings. Risch[6] has shown that, for both monogenic and polygenic traits, models of inheritance can be examined by computing a risk ratio, which compares the prevalence of a trait in relatives with the prevalence of the trait in the population. The more extreme the risk ratio, the more likely a gene for a trait will be

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12 February 1997; 5 June 1997; 12 June 1997

detected, with risk ratios >5 suggesting possible major-gene inheritance. It is clear that prevalence of moderate levels of obesity in families ascertained through an extremely obese member is high;[7,8] however, the specific familial and population rates have not been reported and it has been unclear whether the prevalence of extreme obesity in relatives increases as the obesity in the proband increases. In this paper, we determined obesity risk ratios using a sample ascertained through extremely obese probands and considered practical implications for selecting obesity thresholds for a linkage study.

Materials and methods

Subjects

We recruited members of the National Association to Advance Fat Acceptance (NAAFA). We asked members to provide height and weight for themselves and for their first-degree relatives. The members of NAAFA were mostly female, Caucasian and college educated. A detailed description of the participants has been reported previously.[8]

Obesity index

We used body mass index (BMI, kg/m^2) as an index of obesity.

Age and gender standardization of obesity prevalence and risk ratios

To compute age and gender standardized prevalence rates,[9] we created six categories: three age categories (20–34 y, 35–59 y and ≥ 60 y) for each gender. We then applied an equal weight of 1/6 to the prevalence rate for each age–gender category to standardize the age distribution in the two populations. The weighted, age–gender specific prevalence rates for all first-degree relatives (parents and siblings) of NAAFA probands were totaled and compared with those obtained from the National Health and Nutrition Examination Survey (NHANES) data. In our analysis, we restricted the NHANES group to the Caucasian subjects who enrolled in the first phase of NHANES III and were examined in mobile examination clinics because they were ascertained at the comparable time period (between August 1991 and January 1992) as our study subjects. [10,11]

Risk ratios were calculated by dividing the age and gender standardized obesity prevalence rates in the relatives of probands, by the age and gender standardized obesity prevalence rates in the NHANES III subjects, yielding a standardized risk ratio (SRR). Standard errors were approximated by $1/b[(p(1-p)/n]$, where b is the baseline risk of reaching the obesity threshold in the population, p is the proportion of relatives who reached the threshold, and n is the total number of relatives in the group. To compute standard errors, we assumed family members are independent and the prevalence rates from the NHANES data are constants. Confidence intervals based on the approximated standard errors are anti-conservative and should be considered minimal.

Grouping probands by body mass index (BMI) thresholds to compute standardized risk ratios

We grouped proband BMI in two ways. We first used three ascending, non-overlapping thresholds of obesity in probands (BMIs: 30–39, 40–44 and ≥ 45) to determine whether the risk of obesity in relatives increases with the obesity of the proband (Interval method). We then used three ascending overlapping thresholds of proband obesity ($BMI \geq 30$, $BMI \geq 40$ and $BMI \geq 45$) to assess the overall impact on study design of ascertaining families through probands exceeding various obesity thresholds (Threshold method). We used these thresholds to define obesity in the relatives as well. The thresholds correspond to the 78th, 89th and 99th percentiles in the general population, respectively, and denote moderate to extreme levels of obesity.

Calculation of standardized risk ratios for thinness

We computed age and gender specific SRR for thinness in relatives ($BMI \leq 20$) to determine if thinness in relatives was negatively correlated with the degree of obesity in the proband. Less than 8% of the general adult population has $BMI \leq 20$.

Accuracy of self-reported BMI

For a subset of probands ($n=11$) and their relatives ($n=30$), we measured their height and weight to assess the accuracy of informant's reported values. We computed a Pearson's correlation coefficient between the measured and reported values for heights and weights.

Results

Of the 2444 questionnaires given to NAAFA subjects, 981 (39%) were completed and returned. Respondents were excluded from further analysis if they were adopted, male or had a $BMI < 30$. The remaining 840 respondents (probands) provided information on their 2349 relatives. We restricted our analysis to relatives whose ages ranged between 20 and 74 y to match subjects in the NHANES sample.

Age–gender standardized prevalence rates of obesity among the relatives of extremely obese women *vs* the general population: Grouping probands by BMI interval

The range of obesity thresholds familial risk ratios of obesity in the first-degree relatives increased with

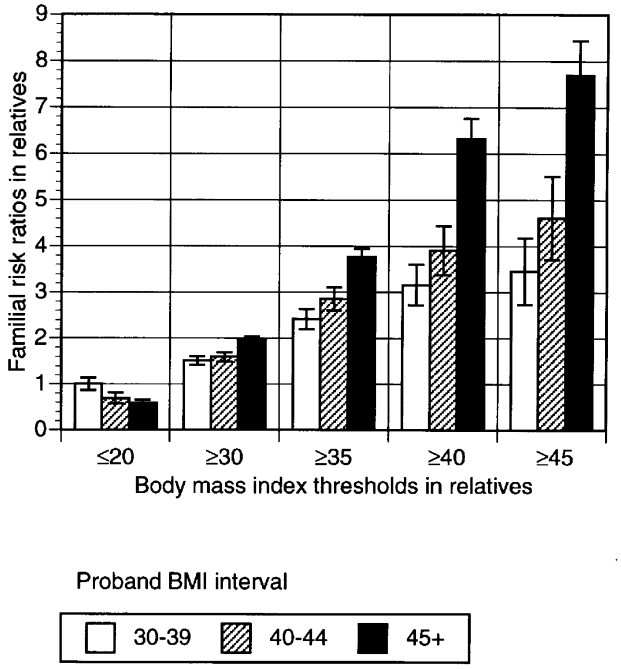

Figure 1 Age and gender standardized risk ratios (SRRs), comparing the prevalence rates of obesity in relatives of probands with extreme obesity *vs* the rates in the population. For three ascending thresholds of obesity, we computed SRRs, stratified by three ascending non-overlapping thresholds of BMI in probands (Interval method). Thinness in relatives was defined as BMI ≤ 20.

degree of obesity in the probands (Figure 1). Moderate obesity (BMI ≥ 30) was significantly more common in the relatives of obese probands than in the population and increased with proband BMI (SRR = 1.5, 1.6 and 2.0 for probands with BMI 30–39, 40–44 and ≥ 45, respectively). Extreme obesity in the relatives (BMI ≥ 45) was much more prevalent than in the population and increased substantially with BMI of the proband (SRR = 3.5, 4.6 and 7.7 for probands with a BMI between 30–39, 40–44 and ≥ 45, respectively). The familial risk ratio for thinness (defined as a BMI ≤ 20) showed an inverse relationship with the probands' BMI. That is, for probands with a BMI 30–39, 40–44 and ≥ 45, the familial risk ratios were 1.0, 0.7 and 0.6, respectively.

Age–gender standardized prevalence rates of obesity among the relatives of extremely obese women and in the general population: Grouping probands by BMI threshold

Table 1 and Figure 2 provide age–gender standardized prevalence rates of obesity for ascending thresholds of obesity in relatives and the corresponding prevalence rates in the general population. Age–gender standardized population prevalence rates, determined from the NHANES sample, were 7.5% for BMI ≤ 20, 21.4% for BMI ≥ 30, 2.4% for BMI ≥ 40 and 1.0% for BMI ≥ 45 (Table 1). Moderate levels of obesity (BMI ≥ 30) were common in the general population; however, in the families of extremely obese women, the prevalence rates of obesity were approximately twice as high as that in the general population (37.7–42.2% *vs* 21.4%). Increasing the obesity threshold to BMI ≥ 40 in the relatives of the extremely obese women resulted in a more than five-fold increase in the prevalence rates of obesity compared with the rate in the general population (11.8–15.1% *vs* 2.4%). When the most extreme obesity threshold was used (BMI ≥ 45), the prevalence rates were nearly eight times that of the general population (6.1–8.0% *vs* 1.0%).

Table 1 Age and gender standardized obesity and thinness prevalence rates[a] for the relatives of obese women and for the general population.

Obesity threshold for proband	*Relatives (n)*	*Relatives (n) with BMI above threshold*	*Age-gender adjusted prevalence for relatives*	*Age-gender adjusted prevalence NHANES III*
Obesity threshold in relatives:	BMI ≥ 30			
≥ 30	2349	916	37.69	21.4
≥ 40	1765	726	39.53	
≥ 45	1235	538	42.02	
Obesity threshold in relatives:	BMI ≥ 35			
≥ 30	2349	548	22.2	6.9
≥ 40	1765	453	24.2	
≥ 45	1235	344	26.1	
Obesity threshold in relatives:	BMI ≥ 40			
≥ 30	2349	283	11.8	2.4
≥ 40	1765	244	13.3	
≥ 45	1235	195	15.1	
Obesity threshold in relatives:	BMI ≥ 45			
≥ 30	2349	145	6.1	1.0
≥ 40	1765	125	7.0	
≥ 45	1235	99	8.0	
Thinness threshold in relatives:	BMI ≤ 20			
≥ 30	2349	114	5.3	7.5
≥ 40	1765	74	4.6	
≥ 45	1235	50	4.4	

[a]Population prevalence rates were obtained from NHANES III Phase 1 (1988–1991) and the population prevalence rates were calculated using all participants who were between 20 and 74 y of age, not pregnant and Caucasian.

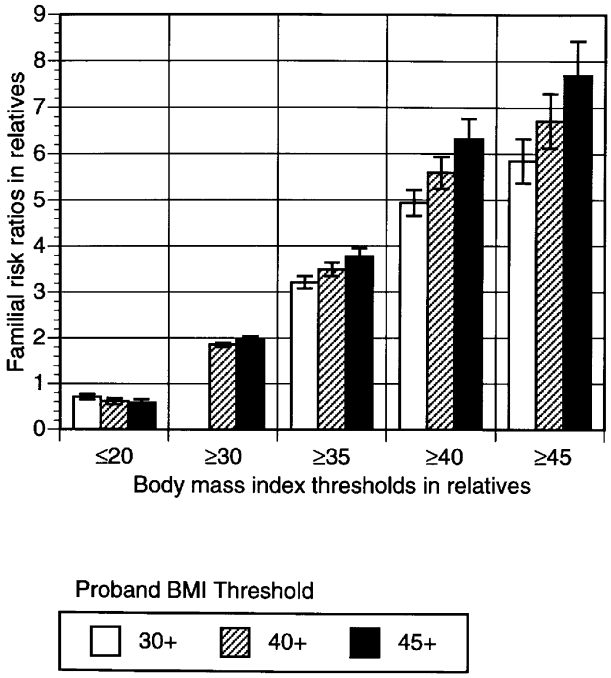

Figure 2 Age and gender standardized risk ratios (SRRs), comparing the prevalence rates of obesity in relatives of probands with extreme obesity *vs* the population prevalence rates of obesity. Ascending overlapping thresholds of obesity of body mass index (BMI) (kg/m^2) were used to define moderate to extreme levels of obesity in the first-degree relatives (Threshold method). Thinness in relatives was defined as BMI ≤ 20.

Accuracy of reported BMI

The recall of height and weight for the relatives of a subset of probands was reasonably accurate: $r_{BMI} = 0.89$, $z = 8.8$, $P < 0.01$. As expected, we observed a systematic underreporting of weight, on average by about 4 kg (10 lb) and an overreporting of height, on average about 2.5 cm (1 in). The net effect is a systematic underreporting of BMI that would have little effect on the placement of individuals in the BMI threshold categories.

Discussion

The familial risk ratio for obesity increased approximately linearly with the probands' BMI, and the risk of extreme obesity in relatives of extremely obese probands (BMI ≥ 40) was more than five-fold higher than in the general population. Selecting families through extremely obese probands with BMI ≥ 40 appears to provide a balance between the competing needs of gene mapping studies: a high familial risk ratio and a sufficiently high population prevalence to make family ascertainment feasible.

Risk ratios and statistical power in obesity gene mapping

Risch[12] extended the work of James[13] and proposed that the recurrence risk in relatives (approximated by SRR in this paper) conveniently provides an estimate for statistical power to detect linkage in studies involving affected relative pairs. Our findings support the usefulness of the λ in genetic studies of obesity.

It is possible to maximise the efficiency of a gene mapping study design by concentrating on probands with extreme obesity (BMI ≥ 40). Risch[6] has suggested that for phenotypic traits with risk ratios > 5, the potential exists for a large proportion of the trait variation to be accounted for by a major gene. For a λ of 5.0, 186 sib pairs are needed to detect linkage (assuming two genes contributing equally and additively, 80% power, one-sided alpha of 0.0001, PIC (polymorphism information content[14]) of 0.8, markers 10 cM apart); however, for a λ of 2.5, more than twice as many pairs are needed to generate comparable levels of statistical power.[12] Therefore, selecting pairs of relatives with higher familial risk ratios increased the statistical power to detect linkage.

Allison *et al*[15] applied the λ statistic to fine gene mapping in obesity to determine the required sample size to localize putative genes. Using the data from published and simulation studies, the authors concluded that λs for milder forms of obesity were disappointingly low. This observation led to the prediction that an impractically large number of sibling pairs would be necessary to achieve adequate statistical power to detect linkage for obesity related genes. In the current study, we examine ways to improve statistical power in obesity linkage studies. We showed that the statistical power can be increased by studying family members with extreme obesity (BMI ≥ 40). If one posits a five gene model (assuming five genes contributing equally and additively, markers 10 cM apart and PIC of 0.8), with a familial risk ratio of 5.0, approximately 569 affected sibling pairs would be needed to detect linkage at 80% power at a one-sided *P*-value of 0.001 and 767 afftected sibling pairs for one-sided *P*-value of 0.0001.[12,16] Even though these numbers are large, they represent significantly smaller sample sizes than those required when families with more modest levels of obesity are ascertained.

Although the benefits of studying more extremely affected probands and their families are straightforward, the rarity of the subjects make them difficult to recruit; therefore, a balance has to be achieved between the decreased need to recruit large numbers of subjects and the increased effort needed to ascertain individuals with more extreme phenotypes. To illustrate this point, we employed an analysis similar to that used by Todorov *et al*[17] and found the costs of screening and ascertaining a family doubles as the minimum proband BMI is raised from 40 to 45. Thus, selecting families through probands with BMI ≥ 40 appears to be the best compromise.

The method of examining extremely discordant sibling pairs has been advocated as a powerful method to map genes for complex traits,[16] but it may be a difficult analytical method for obesity

when extremely obese probands are ascertained.[18] In addition to the relative scarcity of subjects with a BMI ≥ 40, the likelihood that such subjects will have a thin family member is lower than one would expect, based upon population rates. For extremely obese probands, the probability of having a thin first-degree relative (BMI ≤ 20), was nearly half the general population prevalence rate and this further adds to the difficulty of subject recruitment for sibling pairs with extremely discordant BMIs. Without thin siblings, however, families become less informative to detect linkage. As recently suggested, it may be possible to overcome some of these inherent difficulties by raising the threshold for thin relatives to the lower 30% (BMI ≤ 24).[19]

The familial risk ratio provides a heritability index for traits, and it assumes the shared family environment has a negligible influence on the familial aggregation of the trait. This assumption, as it pertains to obesity, has been comprehensively reviewed by Grilo and Pogue-Geile,[20] who concluded that shared family environment has little, if any, effect on the aggregation of obesity within families. So to the extent that familial risk ratios give accurate estimates of genetic susceptibility, our data demonstrate that extreme obesity is more heritable than moderate levels of obesity. This conclusion is further supported by the work of Laskarzewski *et al*,[21] who compared the rates of obesity among families of probands in the upper and lower tertiles of weight-for-height and found the rates of obesity to be much higher in the families with an obese proband. MacLean and Rhode[22] also observed an increased risk of obesity in relatives of patients with extreme obesity by comparing the proportion of proband families that have any relative with BMI ≥ 40 against control families (odds ratio $= 24.5$; 95% CI, 10.4–57.7). Because the unit of analysis in that paper is family rather than individual, it is not a reasonable estimator of λ.

We ascertained families with extreme obesity through members of NAAFA which led to an ascertainment of probands which are over 90% female. Although we restricted our analysis to relatives of female probands, we included both male and female relatives of female probands. The familial risk ratios in female relatives are comparable to those in male relatives (data not shown). Because extreme obesity is less common in men than in women, we predict that familial risk ratios would be higher than the observed familial risk ratios if we had ascertained male probands, selected for comparable BMI values and their relatives.

Accuracy of reported BMI

We used reported values of heights and weights, rather than measured values. Several studies have shown that self-reported values of heights and weights are comparable to those measured.[23,24,25] In a subset of families, we compared the reported values of heights and weights against the measured values, and found the correlation to be reasonably high. As expected, we observed a systematic bias in that respondents underreport BMI. If the results can be generalized to all subjects in our study, the actual risk in first-degree relatives should be higher than the estimated risk based on the reported BMIs.

Conclusion

We observed that the risk of obesity in relatives increased proportionally with the proband BMI, with more extremely obese probands having relatives with more extreme phenotypes. These results suggest that genetic influences are stronger in extreme obesity than in moderate levels of obesity. In genetic studies of obesity, statistical power can be increased by ascertaining families through probands with extreme obesity, with a BMI ≥ 40 providing a good balance between a high familial risk ratio and a high enough population prevalence to make family recruitment feasible. Because the prevalence of thinness was low in relatives of extremely obese probands, the extreme discordant sibling pair method may require raising the threshold for thin relatives.

Acknowledgements

This work was supported in part by NIH Grants R01-DK44073 and R01-DK48095 (RAP) and the St Luke's Hospital/Roosevelt Research Center Core grant (DRR). We would like to thank the members of NAAFA for participating in the survey, Christa Alberry and Elizabeth Joe for collecting data, and Dr David Allison for suggesting a formula for the calculation of confidence intervals for λ.

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